General

Guideline Title

Nonmuscle invasive bladder cancer.

Bibliographic Source(s)

Alberta Provincial Genitourinary Tumour Team. Nonmuscle invasive bladder cancer. Edmonton (Alberta): CancerControl Alberta; 2013 Oct. 29 p. (Clinical practice guideline; no. GU-009). [81 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Genitourinary Tumour Team. Bladder cancer. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Jan. 16 p. (Clinical practice guideline; no. GU-002).

Recommendations

Major Recommendations

American Joint Committee on Cancer (AJCC) staging definitions for bladder cancer are included in Appendix A in the original guideline document.

Management of Ta

Staging

- Complete resection, including muscularis propria, is recommended.

Risk Stratification

Low risk: solitary, primary, low grade pTa
Intermediate risk: multiple or recurrent, large, low grade pTa
High risk: any >pTa, carcinoma in situ (CIS), >low grade

Adjuvant Therapy

- Post-transurethral resection of bladder tumour (TURBT) chemotherapy is recommended for all risk categories of pTa patients, especially for low risk patients, as these patients benefit most in terms of recurrence rates at 2 years.
- The standard of care is adjuvant-immediate chemotherapy instillation post-TUR, unless the bladder is perforated with TUR or if there is a significant risk of vesico-ureteral reflux. Chemotherapy should consist of: epirubicin (100 mg/100 mL) or mitomycin C (MMC; 40 mg/40 mL weekly x 8 weeks then monthly for a year).

- If there is a recurrence, repeat TUR and consider proceeding to intravesical bacillus Calmette-Guerin (BCG) therapy.

Induction and Maintenance Therapy

Induction and maintenance therapy is recommended for intermediate and high risk patients, including those with multifocal tumours or frequent recurrences.

- BCG: induction therapy for 4 to 6 weeks then 3-weekly injections at 3-month intervals; continue for 12 to 24 months, if patient is disease-free at 3 months. Therapy may be continued at 30 and 36 months, at which time a clinical decision should be made as to whether or not to proceed with maintenance.
- MMC: 40 mg/mL monthly; continue for 12 to 24 months.

Second-line Treatment for Ta BCG Failure

- Surgery consisting of aggressive TURBT is recommended.
- Intravesical chemotherapy options include:
  - Interferon alpha-2b (IFN-α2b): 50 million units instillation weekly for 6 to 8 weeks.
    - If residual disease at 3 months (cystoscopy): repeat with a second course at either 50 or 100 million units.
    - If BCG and IFN-α2b failure: 100 million units in 50 mL bladder instillation weekly for 6 to 8 weeks.
  - Gemcitabine: 2000 mg instillation weekly for 6 weeks (induction) followed by 2000 mg instillation monthly for 10 doses (maintenance).
  - Mitomycin C: administer intravesically at a dose of 40 mg weekly for 4 weeks.
  - Consider cystectomy if subsequent failure occurs.

Management of Tis BCG Failure

First-line

- Mandatory repeat TURBT (including muscularis propria) in 2 to 3 months or discussion of immediate cystectomy is recommended.

In the Event of an *Early* BCG Failure

- Surgery is recommended, if the patient is fit.
- Radiotherapy can be considered.
- Staging: upper tract imaging (computed tomography [CT] abdomen/pelvis with contrast) is recommended.

In the Event of a *Late* BCG Failure

- Surgery is recommended, if the patient is fit.
- Radiotherapy can be considered.
- Staging: upper tract imaging (CT abdomen/pelvis with contrast) is recommended.

Management of T1 High-Grade BCG Failure

First-line

- Mandatory induction BCG
- Mandatory repeat TURBT (including muscularis propria) in 2 to 3 months or discussion of immediate cystectomy

In the Event of an *Early* BCG Failure

- Surgery, if fit
- Radiotherapy
- Staging: upper tract imaging (CT abdomen/pelvis with contrast)

In the Event of a *Late* BCG Failure

- Consider reinduction with BCG therapy.

Maintenance Therapy for Ta, T1 High-Grade, and Tis BCG Failure

- Maintenance therapy with the following agents is recommended if the patient is disease free at first cystoscopy:
  - BCG
  - IFN-α2b
  - Mitomycin C
  - Gemcitabine: 2000 mg instillation monthly for 10 doses

BCG Administration

- Start date must be at least 3 weeks after last TURBT
- No liquids x 4 hours prior
- Catheterize patient to ensure bladder is empty
- 1 vial of BCG (PACIS, Immucyst, or OncoTice) diluted in 50 cc normal saline instilled via catheter weekly x 6 weeks
- Patient should hold BCG x 2 hours, rolling every 15 minutes at home before voiding (sitting) into toilet
- Clean toilet bowl with 2 cups of bleach left in bowl for 15 minutes prior to flushing
- Cystoscopy to be performed within 6 weeks of induction

Follow-up

- Cystoscopic evaluation every 3 months for the first 24 months, then annually for 10 years
- Radiological evaluation of lymph nodes and contralateral upper tract as clinically indicated
- Duration: as clinically indicated; cystoscopic evaluation and chest x-ray (CXR) as clinically indicated and then at increasing intervals

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Nonmuscle invasive bladder cancer

Guideline Category

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Internal Medicine

Oncology

Radiation Oncology

Radiology

Surgery

Urology

Intended Users

Physicians

Guideline Objective(s)

To establish best practice for the surgical management of patients with nonmuscle invasive bladder cancer, as well as to describe patient selection criteria for adjuvant therapy, appropriate agents, dosing, and duration of therapy

Target Population

Patients with nonmuscle invasive bladder cancer (i.e., stages Tis, Ta, and T1)

Interventions and Practices Considered

Staging/Evaluation

1. Staging with complete resection, including muscularis propria
2. Risk stratification
3. Computed tomography (CT), abdomen/pelvis (with contrast)

Management/Treatment

1. Transurethral resection of bladder tumour (TURBT)
2. Adjuvant, induction, and maintenance chemotherapy
    - Intravesical chemotherapy instillation (epirubicin, mitomycin C [MMC], gemcitabine)
    - Intravesical bacillus Calmette-Guerin (BCG)
    - Intravesical interferon alpha-2b (IFN-α2b)
3. Cystectomy
4. Radiotherapy
5. Follow-up (cystoscopic evaluation, radiological evaluation of lymph nodes and contra lateral upper tract, chest x-ray [CXR])

Major Outcomes Considered

- 5-year, disease-free, progression-free, disease-specific, recurrence-free, median, and overall survival
- Progression rates
- Presence of residual disease
- Rates of superficial, local, muscle-invasive, or distant recurrences
- Time to recurrence
- Rates of metastasis
- Bladder cancer death rate
- Complication rates
- Tumour-free rate

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

1. What is the appropriate primary therapy for patients with nonmuscle invasive bladder cancer?
2. Which patients are appropriate for adjuvant therapy?
3. Which agents are most efficacious in preventing bladder tumour recurrences?
4. What is the appropriate dosing and duration of adjuvant therapy?
5. How often are follow-up examinations required and for what duration?

Search Strategy

An original guideline on bladder cancer was developed in 2005 and then updated in 2009, 2010, and 2011. The document contained recommendations and evidence on both noninvasive disease and invasive disease. In 2013 the guideline was divided into 2 distinct documents: a guideline on noninvasive disease (GU-009) and a guideline on muscle-invasive and locally advanced or unresectable/metastatic disease (GU-002). The guideline on noninvasive disease includes an update of the original search strategy and recommendations, but incorporates a new literature search and more in-depth recommendations on bacillus Calmette-Guerin (BCG) therapy. The original literature search included the Medline and EMBASE databases. The search term *bladder cancer* was used and results were limited to clinical trials, randomized controlled trials (RCT), and phase III studies. A total of nine citations identified from the original search were relevant to the updated noninvasive bladder cancer guideline.

The search for literature on adjuvant BCG therapy included the PubMed database only, which was searched for relevant literature published between 1993 and 2013 May 28. The search terms *urothelial carcinoma* or *transitional cell carcinoma* or *bladder cancer* AND *bacillus calmette guerin* were used and results limited to meta-analyses, randomized controlled trials, and phase III clinical trials conducted in humans and published in English. The search initially returned 105 citations; further exclusion criteria included studies that did not examine the efficacy of BCG or interventions for BCG toxicity as primary endpoints, studies on prognostic factors only, studies with less than 50 patients in total, older (pre-2000) studies examining toxicity reduction strategies, older (pre-2000) studies comparing a new treatment with BCG as the established standard, as well as previous versions of a Cochrane review, meta-analyses older than 2006 May, phase II trials, retrospective analyses of single RCT data, reviews, and in vitro studies. After applying the exclusion criteria, a total of 60 citations remained and were included in the literature review.

In addition, the National Guideline Clearinghouse database was searched for relevant guidelines published between 2008 and 2013 June 3. The single search term *bacillus calmette guerin* was used. The search returned 3 relevant guidelines from the European Association of Urology, the Scottish Intercollegiate Guidelines Network, and the American Urological Association. Two additional guidelines were identified on the National Comprehensive Cancer Network Web site and the Canadian Urology Association Web site. The American Joint Committee on Cancer (AJCC) staging definitions for bladder cancer was also included as a reference document.

Number of Source Documents

- A total of 9 citations identified from the original search were relevant to the updated noninvasive bladder cancer guideline.
- A total of 60 citations were included in the literature review from the relevant literature published between 1993 and 2013 May 28.
- A total of 5 relevant guidelines were included.

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment and management of nonmuscle invasive bladder cancer

Potential Harms

Adverse/toxic effects of therapy including fever, malaise, nausea, skin rash, allergic reaction, drug-induced cystitis and hematuria

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Genitourinary Tumour Team. Nonmuscle invasive bladder cancer. Edmonton (Alberta): CancerControl Alberta; 2013 Oct. 29 p. (Clinical practice guideline; no. GU-009). [81 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Jan (revised 2013 Oct)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

There was no direct industry involvement in the development or dissemination of this guideline.

Guideline Committee

Alberta Provincial Genitourinary Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, urologists, nurses, pathologists, and pharmacists.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Genitourinary Tumour Team. Bladder cancer. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Jan. 16 p. (Clinical practice guideline; no. GU-002).

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 24, 2012. The information was verified by the guideline developer on February 13, 2013. This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on May 22, 2014.

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